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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/730,575	12/08/2003	Menashi A. Cohenford	11.036011	3067

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EXAMINER	
WOOLWINE, SAMUEL C	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 01/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/730,575	COHENFORD, MENASHI A.	
	Examiner	Art Unit	
	Samuel Woolwine	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *19-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-18, in the response filed on 12/01/2005 is acknowledged. Claims 19-23 are withdrawn from further consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites the use of a "DNA chelating agent". The specification does not define a "DNA chelating agent" or contain this phrase. It is unclear what is meant, since a chelating agent is usually known in the art as a compound which coordinately binds metal ions, such as EDTA. Since it is not clear what Applicant means by a "DNA chelating agent", a broad interpretation will be ascribed for purposes of examination under 35 USC § 102 and 103. Such interpretation will encompass what are traditionally regarded in the art as chelators (e.g. EDTA, EGTA, the zinc-coordinating hexahistidine tag expressed in recombinant proteins, etc) as well as anything that could bind to DNA.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Kurn (U.S. Pat. 6,251,639 B1). Kurn teaches a method comprising subjecting a sample of biological material containing a target nucleotide sequence to amplification using oligonucleotide primers and blockers to create primer extension products that are susceptible to cleavage by double-strand-specific ribonucleases wherein continuous production and cycling of ribonuclease cleaved products allows for amplification of said target sequence (see figures 1A, 1B and 1C and column 4, lines 28-44). Kurn also teaches the method wherein said double-strand-specific ribonuclease is thermostable RnaseH (see column 3, lines 12-22, column 5, lines 25-28, and column 43, line 38).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Richards (U.S. Pat. 5,645,987) in view of Kurn (U.S. Pat. 6,251,639 B1) and further in view of Kacian et al (U.S. Pat. 5,916, 777).

Regarding claims 3 and 10, Kurn teaches a method comprising the steps of forming a mixture comprising a DNA template containing a target, a single chimeric primer that binds to said template, a non-extendable blocker (column 23, lines 12-13

and 54-55) that binds downstream from the chimeric primer, a DNA polymerase which lacks 5' exonuclease activity (column 25, lines 50-54), and a double-strand-specific ribonuclease, and appropriate buffers and nucleic acid precursors (see figures 1A, 1B, 1C, and column 4, lines 28-44). Kurn teaches thermal cycling (see column 3, lines 13-15). Kurn also teaches cleavage and release of the first primer extension product at the ribonucleotide portion of the chimeric primer (see figures 1A, 1B and 1C). Kurn does not teach a chimeric primer comprising a 5' DNA portion and a ribonucleotide base at the 3' terminus (the chimeric primer of Kurn comprises a 5' RNA portion and a 3' DNA portion). Kurn also does not teach using the released product of the first primer extension reaction as a primer in a second primer extension reaction.

Kacian et al teach a method comprising the steps of forming a mixture comprising a nucleic acid template (which template may be either DNA or RNA, see column 3, lines 4-25), a single chimeric primer that binds to said template (see figure 6 and column 3, lines 4-25), a DNA polymerase (see column 3, lines 4-25), and a double-strand-specific ribonuclease (see column 12, lines 12-28), and appropriate buffers and nucleic acid precursors (see column 3, lines 4-25). Kacian specifically teaches a chimeric primer comprising a 5' DNA portion and a ribonucleotide base at the 3' terminus (see column 9, lines 46-66). Kacian teaches the release of the primer extension product after cleavage at the ribonucleotide base of the chimeric primer (see figure 6 and column 12, lines 12-28). Kacian does not teach using the released product of the first primer extension reaction as a primer in a second primer extension reaction. Kacian does not teach the use of "blocker" oligonucleotides or thermal cycling.

Richards teaches a method comprising a "primer extension cascade" in which the cleaved and released primer extension product from a first primer extension reaction serves as a primer in a subsequent primer extension reaction. The product from this second reaction is also cleaved and released (see figure 6). Richards further contemplates the use of the released product from the second reaction as a primer in yet a third primer extension reaction:

> "The applicability of the catalytic oligonucleotide generation method of the present invention can be further broadened if a cascade of substrate reagents [cf. the DNA triggering template of the instant claims] is used. Although a single substrate reagent is sufficient and preferred for traditional purposes of oligonucleotide synthesis, a series of substrate reagents can be employed as a cascade, such that the product from the first level of the cascade catalyzes the generation of product at the second level, *and so forth*" (column 17, line 65 through column 18, line 5, emphasis added).

Richards also teaches:

> "For diagnostic purposes, the final oligonucleotide cleavage product of a target-initiated amplification cascade is used as a measure of the presence of target in a test sample. This final "diagnostic" oligonucleotide product *may be identical or complementary to a portion of the target sequence*, or it may be wholly unrelated in sequence to the target" (column 22, lines 13-19, emphasis added).

Regarding detection of the amplification product (a limitation in claim 10 of the instant application, Richards teaches: "In a typical diagnostic application, the target, although present in minute quantity, is able to initiate the cascade, which then rapidly generates an exponentially greater quantity of final oligonucleotide product which can be measured in a traditional type of detection system" (column 18, lines 12-16).

Richards does not teach a chimeric primer, "blocker" oligonucleotides, or thermocycling. Richards also does not teach RNase to digest the primer extension products or the use of a DNA polymerase which lacks 5' exonuclease activity. The "primer extension cascade" taught by Richards is so similar to the methods claimed in

the instant application as to render the latter obvious. The essential differences between the methods taught by Richards and those of the instant application are that Richards uses the primer extension to create a substrate for restriction endonuclease cleavage, while Applicant uses the primer extension to create a substrate for RNase H cleavage. In both methods, the released primer extension product serves as the primer in a subsequent reaction.

It would have been *prima facie* obvious to one of skill in the art at the time the invention of the instant application was made to incorporate the chimeric primers and RNase H digestion taught by Kacian and the "blocker" oligonucleotides taught by Kurn into the "primer extension cascade" taught by Richards. Kurn provides motivation to use a 5' exonuclease deficient polymerase: "Preferably, the polymerase has little or no 5'→3' exonuclease activity so as to minimize degradation of primer, termination [i.e. blocker] or primer extension polynucleotides" (column 25, lines 51-54). Kurn also provides motivation to use "blocker" oligonucleotides: "...a termination sequence [i.e. blocker] provides the basis for an endpoint for the replication by either diverting or blocking further replication along the template strand" (column 9, lines 60-63). Thermal cycling, as taught e.g. by Kurn (see column 3, lines 13-15) is a common practice in the art for denaturing the products of primer extension to allow for annealing of another primer for a subsequent round of primer extension. Kacian provides the motivation for using a chimeric primer comprising a 5' DNA portion and a 3' ribonucleotide base and RNase H digestion: "The 3'-ribonucleotide primers are preferred, because the are capable of retaining their function after cleavage of the primer extension product to

separate the primer from the oligonucleotide product" (column 9, lines 63-66). In fact, one of skill in the art would certainly have motivation to use the chimeric primer taught by Kacian in view of what Richards discusses in column 8, lines17-62. In essence, Richards remarks that "loss of substrate reagent, due to cleavage of the substrate reagent from cutting attenuation efficiencies of less than 100%, will increase with each cycle" (lines31-33). This problem would be obviated by using the chimeric primers and RNase H digestion as taught by Kacian.

Regarding claims 4 and 11, the DNA polymerase Stoffel fragment of Taq would be obvious to one of ordinary skill in the art as but an example of a thermostable polymerase (as taught by Kurn, column 3, lines 19-22) lacking 5' exonuclease activity (as taught by Kurn, column 25, lines 51-54).

Regarding claims 5 and 12, Kurn teaches the use of thermostable RNase H (column 43, Example 1).

Regarding claims 6, 7, 13 and 14, Kurn teaches thermocycling (see column 3, lines 13-1) as well as carrying out steps of hybridization and enzymatic steps at temperatures ranging from about 25°C to about 85°C (see column 27, lines 6-12). Also, MPEP 2144.05 states regarding the optimization of ranges:

> "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)"

Regarding claims 8 and 15, the essential elements of a polymerase chain reaction are a template nucleic acid, nucleoside triphosphates and/or analogs thereof,

buffers, divalent metals (e.g. $Mg2^{+}$) and a polymerase. All of these elements are part of any method of in vitro enzymatic nucleic acid polymerization, for example as taught by Kurn (column 4, lines 28-44), Kacian (column 3, lines 4-25), and Richards (column 27, Example 3).

Regarding claims 9 and 18, Richards teaches using a molar excess of substrate precursors (functionally the equivalent of the "triggering templates" of the instant claims) in column 16, lines 37-43. Also, it would have been obvious to one of skill in the art to use a molar excess of primers and "triggering templates" in relation to the target, as the law of mass action dictates that the rate of any given chemical reaction is proportional to the product of the activities (or concentrations) of the reactants. In addition, the principle of chemical equilibrium holds that the final concentration of product would be increased by increasing the concentration of one or more of the reactants.

Regarding claim 16, Richards shows in figure 23 the radioactive labeling of the cleaved product of the primer extension cascade. Figures 24 and 25 show the autoradiographic detection of such products.

Regarding claim 17, Richards teaches using a "chelator-metal" complex attached to one strand of the double-stranded nucleic acid as a means of achieving cleavage (see column 9, lines 20-49).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Woolwine whose telephone number is (571) 272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

scw

1/3/06